EXPANDED PROGRAMME ON
IMMUNIZATION

GLOBAL ADVISORY GROUP

MONITORING OF ADVERSE REACTIONS

13th Meeting
14-18 October 1990
Cairo, Egypt

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EPI/GAG/90/WP.12

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Monitoring of Adverse Events Following Immunization in the Expanded Programme on Immunization

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Contents

	page
1. BACKGROUND	1
2. POLICY BASIS	1
3. TYPES OF ADVERSE EVENTS FOLLOWING IMMUNIZATION	3
3.1 **Vaccine-induced Adverse Events**	3
3.2 **Programmatic Errors**	5
3.3 **Coincidental Events**	7
3.4 **Vaccine-potentiated Events**	8
4. MONITORING SYSTEM GUIDELINES	8
4.1 **Overall Objectives of Surveillance of Adverse Events Following Immunization**	8
4.2 **Suggested Monitoring Activities**	8
4.2.1 Objectives	8
4.2.2 Recommended Activities	9
4.3 **Special Situations**	9
4.3.1 Sentinel Surveillance	10
4.3.1.1 BCG Lymphadenitis	10
4.3.1.2 DPT Site Abscesses	11
4.3.2 Enhanced Surveillance	12
4.3.3 Detection of Vaccine-associated Paralytic Poliomyelitis	12
4.4 **Cluster Survey for BCG Lymphadenitis**	13
4.5 **Suggested Standard Case Definitions**	13
5. EVALUATION OF REPORTS OF ADVERSE EVENTS FOLLOWING IMMUNIZATION	13
5.1 **Trigger Events**	14
5.2 **Apparent Clusters of Adverse Events Following Immunization**	15
5.3 **Aids to Evaluation**	16
6. AREAS REQUIRING FURTHER DEVELOPMENT	16
6.1 **Field Manual Guidelines**	16
6.2 **Training Materials**	17
6.3 **Guidelines for Assignment of Probable Cause of an Adverse Event Following Immunization**	17
6.4 **Research Guidelines**	17
6.4.1 Etiological Assessment and Risk Factor Analysis	18
6.4.2 Guidelines for Adverse Event Evaluation of New Vaccines	18
6.4.2.1 Prelicensure	18
6.4.2.2 Postmarketing	18
7. RECOMMENDATIONS	19
REFERENCES	20

Appendix A Rates of Reported Adverse Events Following Immunization
Appendix B Draft Protocol of Cluster Survey for BCG Lymphadenitis
Appendix C Proposed Adverse Events Following Immunization for Which Uniform Case Definitions Are Needed
Appendix D Investigation of Severe Adverse Events Following Immunization, India

Abstract

Adverse medical events occasionally follow immunization with vaccines used under the Expanded Programme on Immunization (EPI). Some of these events are due to the intrinsic characteristics of the vaccines, some can be traced to programme problems such as poor handling or administrative technique, and some occur coincidentally after immunization due to other causes. The detection of serious adverse events following immunization (AEFI) is important to the success of a programme since the occurrence of such events can be influential in community acceptance of immunization. In developing programmes, the majority of substantial complications recognized following immunization appear to be programme-related. The underlying causes need to be identified and corrected; if allowed to continue, they will seriously undermine the credibility of the immunization services. As a positive step in programme management, all EPI areas should monitor for selected adverse events following immunization. In most areas, the priority will be to examine events that cause community concern for programmatic errors that can be prevented, such as DPT abscesses and reported deaths, due to unknown causes, temporally associated with immunization. In selected areas, more effort can be put into examining less common, purported inherent risks of vaccines. Several of these activities can be undertaken immediately. Recommended activities include routine monitoring by health workers giving immunizations of reports of abscesses or BCG lymphadenitis; solicitation of reports from primary care physicians and hospitals of vaccine-associated abscesses, illnesses requiring hospitalization, and deaths; and use of sentinel surveillance. Investigation and evaluation guidelines are suggested. An eventual goal for all programmes would include routine compilation of information related to adverse events following immunization in the country. Monitoring methods will vary among countries. Sharing of information will be beneficial for all EPI programmes, beginning with currently available information. Issues that should be addressed further include the development of field guides and training materials reflecting these activities, and guidelines for research in vaccine safety.

1. BACKGROUND

The focus of many immunization programmes has been to provide vaccines to all eligible children by progressively increasing coverage. The vaccines used under the Expanded Programme on Immunization (EPI) are effective and safe. This is documented by decades of experience worldwide. However, just as no vaccine is perfectly effective, none is entirely without risk; therefore, the occurrence of some adverse events following immunization is expected.

Many types of adverse events following immunization (AEFI's) can be seen. Some of these events are due to the intrinsic characteristics of the vaccines. Some events can be traced to programme problems such as poor handling or administrative technique. Additionally, some medical events will occur coincidentally after immunization; that is, they are not due to immunization and would have happened even had the child not been vaccinated.

Most of the truly vaccine-induced AEFI's are mild, relatively common and temporary. The more severe vaccine-induced AEFI's, whose precise rates are often difficult to estimate, are a mere fraction of the complications resulting from the natural disease itself. This is true for all EPI antigens. The benefits of immunization greatly outweigh the risks of these rare serious vaccine-associated events.

Serious AEFI's have been recorded as a result of mishandling of vaccines and poor administrative techniques. In rapidly developing programmes, AEFI's due to programmatic causes may predominate. Surveillance and investigation of these events can help to identify problems requiring correction. Such avoidable events can be minimized through early recognition, retraining, improved field supervision and logistic support.

The EPI vaccines are given to children at an early age when acute viral and bacterial infections are common. Additionally at this age, some neurological syndromes can occur spontaneously or be due to causes unrelated to immunization. If there is a histor of immunization in the recent past, these temporally-related events are often assumed, incorrectly, to be due to the vaccine, especially if a similar non-specific syndrome is also known to occur after immunization.

As coverage levels increase and the incidence rates of the vaccine-preventable diseases and their complications decline, there is an increase in the relative importance of adverse events following immunization due to factors other than programmatic errors. This results from increasing recognition of adverse events due to immunization as well as detection of coincidentally occurring adverse events through improvements in the surveillance systems. Even in areas where the vaccine-associated events may appear to be relatively more frequent than disease sequelae, the risks of immunization are greatly exceeded by the benefits because of the large numbers of complications and deaths prevented by immunization.

2. POLICY BASIS

It is important that documented vaccine-induced adverse events are recognized as inherent risks of immunization. The detection of serious AEFI's is important since the occurrence of such events can influence community acceptance of immunization and the success of an immunization programme. The data collected through the monitoring of AEFI's is information for action. The first purpose of monitoring AEFI's in developing immunization programmes is to identify and subsequently avoid programmatic errors. Second, it is important to document severe AEFI's to assure the community of the relatively low risk to immunized children of experiencing an adverse event. The community members must be convinced that the exposure of an individual child to a serious AEFI due to vaccine is extremely rare and that if coverage levels fall due to perceived fear of AEFI's, the risks of complications due to natural infection to all children would increase many-fold.

In developing programmes, with the priority being achievement of high coverage levels as rapidly as possible, monitoring of AEFI's might at first appear as an additional burden on an overloaded system. However, in such areas, the majority of serious AEFI's recognized following immunization appear to be programme-related. If allowed to continue, they will seriously undermine the credibility of the immunization services. Moreover, some events, like injection site abscesses, are indicators of deficiencies in the system which could potentially lead to more severe, sometimes fatal, complications, unless corrected. Additionally, AEFI monitoring provides a means of communicating with members of the community; investigation of a severe AEFI that parents or the community feel is related to immunization will often lead to evidence of its being vaccine-induced (and rare) or coincidental, sufficient to satisfy their concerns and maintain confidence in the health system. Even if the investigation is not successful in identifying the probable cause, the mere fact that action has been taken will help to allay public fears.

In most developing immunization programmes, health workers have achieved remarkable success under enormous pressures and constraints. The health staff need moral support and guidance from their supervisors should a serious AEFI occur in their area. Even when the event appears programme-related, health workers should be encouraged to report such events so that the underlying cause can be identified and corrected. For instance, the occurrence of infections related to the use of contaminated needles may be occurring not because of lack of appropriate training but because of limitations in sterilization equipment.

Monitoring systems for AEFI's will differ depending on the needs and resources. Some events can be incorporated in the routine surveillance system for vaccine-preventable diseases. For the more severe events leading to hospitalization or death, health personnel should be alerted to report immediately the special event following immunization to the appropriate local health office. The more advanced systems may wish to incorporate additional events for study of risk factors or document indices of events per doses administered, for which enhanced surveillance systems may be required.

Many countries are currently monitoring adverse events only sporadically and informally. In several other countries a great deal of information has been collected and assimilated. As countries strengthen their systems for monitoring AEFI's, they should to share experiences and exchange information. WHO can play an effective role in compilation and dissemination of available data, as is currently done for drug manufacturers' reaction report data by the Council for International Organization of Medical Sciences with Adverse Drug Reactions. Field guides will need to be developed to encourage uniformity in methods to facilitate monitoring and investigations. These may need to be adapted to suit country needs.

3. TYPES OF ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

3.1 **Vaccine-induced Adverse Events**

Vaccine-induced adverse events are unavoidable risks of any immunization programme due to the intrinsic characteristics of the vaccine and the individual responses of the child. Most of the adverse medical events commonly induced by vaccines are mild and of short durations. These may be mild systemic reactions such as fever, rash and mild lymphadenopathy, or local reactions like redness, tenderness and pain at the injection site. Such reactions do not lead to lasting injury to the child. Although, when within average rates, these reactions have not seriously affected acceptance of immunization services nor have they been a major cause of high dropout rates, they have a potential to do so in some areas particularly if the severity of the reactions or the rates increase. A number of factors can increase the frequency of these reactions, including a change in manufacturing procedures or vaccine strains, or programmatic issues. Included in those adverse events that are primarily vaccine-induced but also may be affected by programmatic errors are sterile abscesses following Diphtheria-Pertussis-Tetanus (DPT).

Bacille Calmette Guerin (BCG) vaccine is associated with a number of adverse events. Suppurative lymphadenitis following BCG vaccine is usually self-limiting and has been reported in 0.1% tc 4% or more (commonly 1-2%) of immunized children under 2 years of age. The risk of adverse events is particularly related to the BCG strain used by different manufacturers which reflects the level of attenuation. Additional factors affecting the rate of adverse events are the dose, the age of the child, the method of immunization and the skill of the vaccinator. Observed rates of suppurative lymphadenitis vary widely by country and preparation of vaccine used. There has been a recent series of outbreaks of lymphadenitis after BCG vaccine. Every outbreak reported to WHO has occurred following a shift of vaccine from a more to a less attenuated vaccine strain, most often to Pasteur strain vaccine. Pasteur Vaccins has recently decreased the antigen content of its vaccine for neonatal immunization which may result in less frequent lymphadenitis.

The most serious complications of BCG immunization are disseminated infection and osteitis, which are both rare. The former is generally related to severe abnormalities of cellular immunity, including symptomatic infection with the Human

Immunodeficiency Virus; the latter has been reported mainly among infants immunized in the neonatal period with the Goteborg strain no longer used (up to 46 per million children). With the other strains now in use, rates of 0.1 to 0.6 per million immunized children have been reported.

Moderately severe vaccine-induced adverse events uncommonly follow immunization, such as measles vaccine-associated seizures or DPT-associated seizures or collapse (hypotonic hyporesponsive episodes). Recovery appears generally to be complete in children experiencing these AEFI's, but some clinicians disagree. Rarely, measles vaccine-associated encephalitis occurs and could possibly result in permanent disabilities. Although investigations can be inconclusive and these AEFI may be largely unavoidable, reporting and follow-up of the severe events are necessary to confirm low incidence.

The most serious events reported in the medical literature temporally related to DPT or pertussis vaccine immunization are severe neurological illnesses. Similar syndromes may also be seen in non-immunized children, often making it difficult to distinguish between vaccine-induced versus coincidental event. In the first controlled study of the issue, performed in the United Kingdom, it was estimated that a serious acute neurological illness occurred once in 140,000 DPT injections and that permanent sequelae occurred once in 330,000 doses. However, many other recent studies examining the issue have failed to implicate pertussis vaccine in inducing acute encephalopathy or other serious acute neurological illness. It is uncertain whether an acute encephalopathy can be attributed to DPT, since the evidence is inconsistent. Most scientists reviewing the United Kingdom study indicate that the results are inconclusive regarding whether DPT causes permanent neurological damage. If DPT is ever causally associated with permanent damage, it is apparently a much rarer event than previous estimates indicated.

The occurrence of vaccine-associated paralytic poliomyelitis following Oral Poliovirus Vaccine (OPV) is an example of a documented rare risk. WHO has monitored vaccine-associated poliomyelitis through the Consultative Group on Poliomyelitis Vaccines, to whom vaccine-associated paralytic disease was reported by selected participating countries during the period 1970-84. These studies have confirmed the extremely low risk of vaccine-associated paralysis. Generally, cases of flaccid paralysis persisting more than 42-60 days (or where death intervened or no information was available) have been considered clinical poliomyelitis. Those polio cases occurring within 7-30 days of OPV receipt were classified as vaccine-associated when not in epidemic situations. Studies in the USA have estimated a risk of one case of such paralysis per 1.2 million children immunized; if contact acquired cases are included, the estimate is one case per 500,000 children immunized. In areas still experiencing substantial endemic poliomyelitis, classification of vaccine-associated illness is not possible.

Other rare vaccine-induced complications have also been described, including allergic reactions, which are extremely low-risk vaccine-induced AEFI's. These may occur due to the antigens

themselves or other components such as egg albumin, antibiotics or preservatives.

The rarity of severe adverse events and the fact that similar syndromes also occur irrespective of immunization makes investigations and collection of precise data difficult. Controlled studies can be difficult to perform and many risks have been estimated without appropriate control comparisons. In addition, case definitions, investigation methodologies and local risk factors differ, making it difficult to compare rates or pool data. Despite these limitations, rough estimates of reactions following immunizations shown in Appendix A confirm the wide variations in complication rates following immunizations and those following natural disease; please note the text above regarding some recent observations for some of these rates.

Table 1. Adverse Events following Immunization

A. Vaccine-related - no vaccine is perfectly safe
   * - mild and common
   * - Severe and rare
     o suppurative lymphadenitis
     o shock/collapse
     o paralytic polio
     o osteitis
     o encephalopathy?
     o encephalitis

B. Programmatic - due to mistakes in administration
     o septic death
     o abscesses
     o suppurative lymphadenitis
     o severe local reaction
     o substitution

C. Coincidental - not due to immunization, temporal
     o encephalopathy/encephalitis
     o SIDS

3.2 Programmatic Errors

Rapid increases in immunization coverage levels have been recorded worldwide. Growth of EPI has sometimes resulted in extension of immunization services in areas where logistic support and training programmes may not have been adequate and monitoring systems relatively weak. In addition, turnover of peripheral health workers is common to all programmes. Under such situations, AEFI's have been observed due to improper or inadequate sterilization of equipment, incorrect doses and routes of vaccine administration, or substitutions of drugs for diluents or vaccines. In many countries, the proportion of serious AEFI's due to programmatic errors may exceed the coincidental and vaccine-induced adverse events. Awareness about and investigation

of such events is important to identify quickly the underlying cause, as they are avoidable if problems are corrected. Moreover, unlike severe vaccine-induced AEFI's of which individual occurrences are unpredictable, AEFI's due to programmatic errors can be expected in areas where vaccine administration guidelines are not being followed. Such reactions can severely damage the credibility of the health services, especially if deaths have resulted.

The most common manifestation of a technical problem is a DPT vaccine-associated site abscess. There are two types of abscesses. Bacterial abscesses are the result of contamination indicating local problems in management of sterilizing equipment, reuse of syringes and needles and/or inadequate field monitoring. Sterile abscesses are a rare consequence of vaccines containing aluminum salts, particularly DPT. Although sterile abscesses normally may be expected at an approximate frequency of once in 100,000 injections, inadequate shaking of the vaccine before use, subcutaneous injection, and/or perhaps the use of vaccine that has been frozen can affect the rate. The vast majority of abscesses that will come to light in most EPI programmes will be bacterial and can be expected to be due to problems related to field implementation. Supervisory staff should follow-up promptly. Abscesses also require medical attention. In rare instances, in the absence of adequate medical care, bacterial abscesses are known to have resulted in death.

Just as bacterial abscesses and septicemia can result from DPT contamination, AEFI's related to contamination can apparently also occur with measles vaccine. During the period 1985 to 1988, 17 reported incidents of single cases or clusters of clinical toxic shock syndrome occurred following measles immunization in India. This was a period when measles vaccine was introduced on a large scale in the country, during which 26 million vaccine doses were administered. All affected children had similar symptoms of abrupt onset of fever, vomiting and watery diarrhoea within a few hours of immunization, often leading to death within 24 hours; 43 deaths occurred. These reports were received from different parts of the country at different seasons of the year, and different batches of vaccine were involved in each. Programmatic errors were highly suspected after the first reports, since most cases occurred in clusters of 2 or more following a given vaccination session. In every situation, evidence was found of use of unsterile syringes and needles or reuse of opened vials; Staphylococcus aureus was isolated from a few available implicated vials. Preventive measures included ensuring full supply of needles, syringes and sterilization equipment and retraining of health personnel, re-emphasizing the use of separate sterile syringe and needle for each injection. As a result, the reported number of such events has sharply declined. Rare cases have been reported since 1988. As an additional precautionary measure, the medical officers at the peripheral treatment facilities were alerted to treat any child with fever, vomiting and profuse watery diarrhoea after measles immunization as a medical emergency. Although the precise cause of these incidents could not be clearly identified, the most likely reason was the contamination of measles vaccine vials.

The EPI vaccines have been used successfully for many years. Sometimes, however, a change in the source of the vaccine can increase the percentage or severity of local reactions, some of which can highlight programmatic errors. After a change of the vaccine strain (manufacturer) of BCG vaccine in Zimbabwe, an increase was noted in the number of reports of lymphadenitis occurring within 3 months of BCG administration in neonates. Although the clustering was related to the change in the strain of BCG used, previously overlooked programmatic errors were discovered, including deficiencies in reconstitution and administration techniques. By retraining of field workers and by assisting the health workers in supportive counselling, potential damage to the immunization programme was minimized. Nonetheless, the Ministry of Health elected to return to the vaccine strain used previously.

Use of dangerous drugs in place of vaccines or to reconstitute vaccines is extremely rare. The possibility exists because many medications are packaged in vials and ampoules similar to vaccines or their diluents. Such incidents have been reported in places where staff were inexperienced and poorly trained, and in large hospitals where vaccines were stored together with potentially dangerous drugs in the same refrigerator. In three examples, muscle-paralysing agents were mistakenly administered. In the first two situations, succinylcholine was used in place of DPT with several cases of resultant apnea and death. In another instance, in one hospital 7 children became cyanotic and floppy, including two with respiratory arrest, 15 to 20 minutes after BCG administration. There were no fatalities. Pancuronium bromide, a curare-like drug, has been substituted for the diluent of BCG.

Another programmatic error rarely resulting in AEFI's is lack of adherence to contraindications of immunization. Vaccinators should not give an EPI vaccine to a child who has had a severe (possibly vaccine-induced) event after a previous dose, or give BCG to a child with symptomatic infection with the Human Immunodeficiency Virus. Whether giving additional DPT doses to a child who had a seizure or any other short-term event after DPT has any lasting consequence has not been established. Serious AEFI's that occur as a result of programmatic errors, such as bacterial abscesses, are not contraindications to further doses.

3.3 Coincidental Events

The EPI vaccines are usually administered to children at an age when infections and other illnesses are common. Some adverse events reported following immunization may have only a temporal relationship to immunization, the primary cause being obviously unrelated to vaccine administration, an example being pneumonia following DPT. Unless such events cause undue concern, either among the peripheral staff or the community, a more thorough investigation may not be necessary. Events leading to death, permanent disabilities or prolonged hospitalization are of more concern, particularly if these events are similar to the rare vaccine-induced risks.

Through enhanced surveillance systems many deaths reported following immunization currently in industrialized countries are Sudden Infant Death Syndrome (SIDS), death under one year of age

without known cause but often with characteristic pathological findings. Recent research has failed to implicate administration of DPT in SIDS deaths. The age distribution of DPT immunization in the first year of life and age distribution of SIDS are very similar in many areas, making coincidental temporal association a frequently expected event. In other deaths in industrialized countries, vaccines are rarely implicated as causal.

Although investigations may not always identify the primary cause or provide enough evidence to rule out vaccine relationship, these should be considered if resources permit, to allay public fear and maintain credibility. When a previously healthy child has a severe medical event following immunization, the parents or community will often assume the vaccine as the cause; therefore, health systems should be responsive to public complaints.

3.4 Vaccine-precipitated events

Some AEFI's may actually be considered to be related to receipt of vaccine, and probably would have occurred at some later time but occurred sooner because of immunization. An example of this is a simple febrile seizure following immunization in a predisposed child (that is, with a family history of simple febrile seizures). This category of AEFI's may include many illnesses, but is controversial; this document will not refer to it further.

4. MONITORING SYSTEM GUIDELINES

4.1 Overall Objectives of Surveillance of Adverse Events Following Immunization

The purposes and priorities of adverse event monitoring will change as a programme develops. Early in the development of EPI, problems with programmatic errors will be the major reason for significant numbers of adverse events following immunization; the vaccine-induced adverse events will be less significant. Most instances of vaccine or needle/syringe contamination will be manifest as abscesses. Because of the relationship of abscesses to the immunization site, many cases of abscesses should come to the attention of the health worker. Other cases may require finding using the health care system.

As an EPI programme makes improvements in coverage and management, problems with programmatic errors will occur with lower frequency, while events resulting from inherent risks of vaccines and/or coincidental events may eventually exceed the complications of the diseases. As the surveillance needs change, the emphasis of various surveillance system components will need to be changed. In all EPI programmes, monitoring of adverse events following immunization will be able to strengthen the integrity of the immunization programme by allowing earlier detection of problems.

4.2 Suggested Monitoring Activities

4.2.1 Objectives

a) Detect programmatic errors, including manifestations of contamination of vaccine or needles/syringes, possibly including septic death;

b) Detect rare severe vaccine-induced illness, such as anaphylaxis;

c) Detect other serious adverse events following immunization which could have an impact on immunization programme success to ensure that early investigation is undertaken.

Table 2. Surveillance System for AEFI

A. All programmes

* Routine
  - o Abscess

* Immediate, special
  - o Severe events requiring hospitalization
  - o Death

* Sentinel
  - o Lymphadenitis
  - o DPT site abscess

B. Advanced programmes

* Routine (enhanced)
  - o Abscess
  - o Lymphadenitis
  - o Febrile/afebrile seizures
  - o Encephalopathy

* Immediate, special
  - o Severe events requiring hospitalization
  - o Death

C. Special surveillance

* Vaccine-associated paralytic poliomyelitis

4.2.2 Recommended Activities

a) Vaccinator: Report local abscesses at the DPT immunization site, instances of draining lymphadenitis of the BCG vaccinated limb, or any other adverse event following immunization that comes to her (or his) attention, to supervisors on a routine basis, along with disease reporting and dose administration data.

b) Primary care physicians: Report all DPT site abscesses that occur within 2 weeks of immunization and draining lymphadenitis at any time after immunization to district health officers;

OPTION: in sentinel sites, this could include negative reporting of these events (see 4.3 below).

c) Primary care physicians and hospitals: Report all apparently vaccine-related deaths and hospitalizations that occur within 48 hours (or 1 week) of any immunization to district health officers.

d) Supervisors: Monitor the community for rumors of vaccine site abscesses or other adverse events.

e) Managers: compile these data centrally for each diagnostic class of AEFI and disseminate this information to field personnel. Eventual compilation in each WHO region.

OPTION: in certain countries, it may be more appropriate for there to be entirely local responsibility of investigations of site abscesses and BCG lymphadenitis, without centralized reporting, until all areas in a country approach similar status.

4.3 Special Situations

4.3.1 Sentinel Surveillance

Sentinel surveillance can be used to monitor all substantial AEFI's using existing sentinel sites for vaccine-preventable diseases, such as hospitals with large pediatric outpatient departments and MCH clinics where children with adverse events are more likely to be seen. It would be of higher value when negative reporting is included and the number of children seen who are recently immunized can be estimated.

Sentinel surveillance can be of particular value in detection of AEFI's when

1. the events are highly specific for being either vaccine-induced and/or programmatic errors, and
2. they are frequent enough so that the system would be likely to detect them.

This is the case for BCG-associated lymphadenitis (with or without drainage); it may also be the case for DPT site abscesses. Additionally, the Lot Quality Assurance method can then be applied to estimate the maximal likely rate of these events (see Table 3).

4.3.1.1 BCG Lymphadenitis

Sentinel surveillance could be of particular value when used to monitor routinely the risk of BCG lymphadenitis. Routine examination at sentinel sites could be performed for BCG lymphadenitis in children who were immunized with BCG 4-6 months previously and who make health care visits for other reasons. Although not truly population based (but rather influenced by

factors that determine whether a given child has access to care), such surveillance would nonetheless provide an index of these events if the number of children seen at the surveillance site who were immunized with BCG 4-6 months previously can be estimated. The results of several sentinel sites could be compared or pooled.

Estimating the maximal likely rate of adverse events following BCG can be more accurately performed for a larger area using cluster survey techniques in the whole population base. See Section 4.4 below.

Table 3. Maximal Estimated Rate* of Adverse Events Following Immunization, Based on Size of Surveyed Sample and Number of Events Observed in Survey

	Number of Events Observed in Sample				
No. in sample	0	1	2	3	4
250	1.5%	2.3%	2.9%	3.5%	4.1%
300	1.2%	1.9%	2.4%	2.9%	3.4%
350	1.0%	1.6%	2.1%	2.5%	2.9%
400	0.9%	1.4%	1.8%	2.2%	2.5%
450	0.8%	1.3%	1.6%	1.9%	2.3%
500	0.7%	1.1%	1.5%	1.7%	2.0%

*with 5% chance of it being higher (upper 95% confidence limit of binomial distribution)

4.3.1.2 DPT Site Abscesses

Sentinel surveillance can be of value in supervising new health workers or those who previously had problems by monitoring for site abscesses following DPT for children immunized 2-4 weeks previously. For example, if 450 children recently immunized with DPT are seen at a given site in a month and no abscesses are seen, the rate of occurrence is no more than 0.8%. If any cases are detected, follow-up of other children in the area of such affected children is indicated.

4.3.2 Enhanced Surveillance

Many countries in North America and Europe such as Canada, United States, Denmark, Federal Republic of Germany, France, Switzerland, Netherlands and the United Kingdom have enhanced passive reporting systems for monitoring vaccine safety. Selected areas or countries may elect to increase illnesses under surveillance and ascertainment. If the objective is determining whether a reported non-specific adverse event occurs after immunization at a more frequent rate than expected, it must be clear that the indices so estimated are crude approximates of total rates of illness (vaccine-induced plus coincidental causes) because

1. even with enhanced surveillance, only a fraction of all adverse events that occur are reported;
2. most importantly, of the events that are reported, substantial reporting biases may be present;
3. the rates of occurrence of certain non-specific events in the absence of immunization are frequently poorly estimated and vary widely by population; and
4. the denominator data on number of doses administered or distributed may not be accurate.

Additional objectives of this surveillance are to detect unusual or rare instances of adverse events following immunization (vaccine-induced and/or coincidental) and to highlight the possible needs for further controlled investigation of vaccine causation in selected associated events.

If enhanced surveillance is selected, the following may be substituted for/added to the above methods:

a) Parents: asked to report any serious illness that occurs within 4 weeks of immunization to the immunization center, who routinely reports to a centralized reporting site;

b) Vaccinator: routinely examines vaccine site and routinely questions parents regarding certain events, such as seizure, upon return for the next immunization;

c) Manager: evaluate reports from any other means, such as laboratory reports of paralytic poliomyelitis or other indirect reports.

4.3.3 Detection of Vaccine-Associated Paralytic Poliomyelitis

Industrialized countries have undertaken classification of paralytic poliomyelitis cases based on epidemiological evidence, supported by laboratory findings. This requires collection of separate fecal specimens within 6 (preferably 2) weeks of onset of paralysis for poliovirus isolation, typing and strain characterization by appropriate methods. Laboratory investigation of specimens from all reported cases of flaccid paralysis is now also being done in South and Central America. It is now WHO policy, because of the Initiative for the Global Eradication of Poliomyelitis, that isolates, especially in areas with very limited numbers of poliomyelitis cases be investigating to characterize the causative virus. Isolation of vaccine-like polioviruses from cases without recent immunization indicates possible contact cases. Access to laboratories to perform this

work is now being assured in all countries with limited transmission of polio.

In countries and other areas still experiencing endemic and epidemic poliomyelitis, classification of vaccine-associated poliomyelitis is not possible. Because of problems in timing of specimen collection and particularly the ability to identify co-infections, isolation of vaccine-like poliovirus from a recently immunized child with clinical paralytic poliomyelitis can be anticipated in a high proportion of cases caused by wild poliovirus.

4.4 Cluster Survey for BCG Lymphadenitis

The maximal likely rate of BCG lymphadenitis can be documented by a cluster survey. A random sample of 400 children who received BCG is selected and reexamined 3 months later for lymphadenitis. The 30-cluster method of selection and the Lot Quality Assurance statistical method is used. The sensitivity of the method has not been tested (see Appendix B for draft protocol).

4.5 Suggested Standard Definitions

Appendix C lists for specific adverse events reported in the literature associated with immunization, not all with causal evidence, for which standard case definitions should be developed. Timing need not be specified generally in these definitions. Exceptions to this are certain specific syndromes with known prolonged incubation periods, such as vaccine-associated poliomyelitis and BCG lymphadenitis, in which AEFI's can occur over a long period of time; for these, the definitions should be time-specified. The timing between immunization and onset of most adverse events of interest may be varied for surveillance purposes, and in assignment of probability of cause.

Particularly in regard to non-specific systemic adverse events following immunization, these definitions would be intended for use in event categorization, including when death results. Such categorization implies the collection of sufficient information c which to base it. Monitoring of events would have to make use of wider, less specific definitions in order to have a sensitive surveillance system. Those programmes without current monitoring systems for AEFI's should focus on specific vaccine-induced events.

5. EVALUATION OF REPORTS OF ADVERSE EVENTS FOLLOWING IMMUNIZATION

Independent of the level of monitoring of adverse events following immunization, managers of EPI programmes should be prepared to receive reports of apparent clusters of adverse events following immunization or single reports of certain selected 'trigger' events requiring action. The basic principles of field investigations of infectious diseases need to be followed. The data are collected in order to make decisions -- decisions about the cause of the problem (is it focal, multifocal or global in scope?) and decisions on what action is called for. Prior to

taking action, investigations of these apparent clusters or trigger events will be necessary to

1. examine the clinical data to confirm the diagnoses and outcome;
2. search for whether additional similar vaccine-associated cases can be detected;
3. examine which specific vaccine errors in handling or administration techniques could be implicated by the reports; and
4. suggest the need for further data collection, such as whether similar problems are being observed in children not recently vaccinated, laboratory data, etc.

As with any outbreak investigation, repeated examination of the data on hand will be necessary. If several cases of a serious event are reported (or discovered on investigation of a single report), the possibilities of coincidence, vaccine-induction or errors at many levels of the delivery of immunizations must all be considered. Obtaining this information rapidly requires that programme managers be in frequent contact with health workers and/or supervisors. Transferring information for later review by persons who will not have the advantage of first hand experience with the clinical and programme particulars requires a fully detailed investigation report; an example of the contents requested in reports in India is included in Appendix D. Other country managers may wish to develop their own or adapt this for their specific needs.

5.1 Trigger Events

Single reports of certain vaccine-associated events should trigger further investigation. Examples of these on a less urgent basis are some specific events, such as draining lymphadenitis cases and DPT site abscesses. Because a report of a single site abscess could indicate many others occurring but unreported, these could be investigated by local staff in a timely manner whenever resources allow, by reviewing outcomes in other children recently immunized by the health worker and perhaps other workers in the surrounding area, and by reviewing technique.

For major non-specific events following immunization, such as deaths and hospitalizations, particularly if associated with site abscess or fever, central notification is recommended and an urgent investigation is necessary.

1. to examine for the possibility that vaccine handling or administrator error is a cause, such as bacterial contamination, diluent substitutions, etc. If technique or technical problems are discovered, programme managers will need to identify what steps can be taken to prevent such an occurrence in the future;
2. to indicate to parents and community the programme's interest in monitoring vaccine-associated events;
3. to determine likely reasons for death, if unrelated to immunization, in order to help allay fears. Sufficient data should be collected to allow scrutiny to either infer or rule out programmatic errors, if possible.

Managers should anticipate that they will not always find obvious reasons for AEFI's, and should be prepared to explain this to the parents and community. Expert panels of clinicians and other scientists aware of the medical literature may be of value in reviewing such cases.

In some programmes monitoring AEFI's, other medical events will be reported that may require different investigative responses, particularly those in which the children rapidly recover. Medical events such as seizures are relatively common in the population, independent of immunization (monthly incidence at 3-15 months of age of 0.8-1.4/1000 children), besides being known consequences of immunization; thus, single reports of these following immunization do not warrant investigation beyond collection of data and counselling of parents.

5.2 Apparent clusters of vaccine-associated events

Immunization programme managers must maintain a high index of suspicion to consider life-threatening AEFI's or any unusual AEFI's in clusters of two or more as a possible manifestation of real problem. This problem could be a programmatic error at the health worker or primary health care center level, such as use of a drug for vaccine diluent or, theoretically, beyond the level of the health worker, such as a problem with a batch of vaccine. As indicated above, further investigation may indicate additional cases, in the children vaccinated by the same vaccinator or in others. Central notification of apparent clusters and confirmed clusters is imperative. Whenever reports of severe events are received, it would be prudent to examine the lot numbers and assess other areas where the lot(s) have been distributed. Although lot-related concerns have been raised in some situations, only rare examples of true lot-specific problems have been recorded.

When clusters are discovered and confirmed, but programmatic difficulties not established, deciding whether the cluster is truly related to the immunization may be very difficult. The complexity is derived from determining whether more cases are being reported in vaccinees than would be expected by coincidence alone. Investigations of surrounding areas may be necessary to confirm that similar problems are not being seen in a comparison group of children not recently immunized. Use of the Poisson distribution as a statistical tool may be helpful but requires estimation of the expected frequency of the event. Additionally, there may be a possibility of a statistically significant cluster due to chance alone, as well as the possibility of incomplete and biased case finding. Such circumstances could occur with illness unrelated to administration of vaccine, such as pneumonia, or with diagnoses that may indeed be related to immunization. The primary concern is to detect AEFI's that might be related to programmatic errors and collect enough information to take action.

Selected special studies can be helpful in deciding whether a cluster of a given reported event, such as a septic death, or a previously unrecognized event, such as sudden apnea, is related to a given vaccine session (or given vaccine lot). In order to avoid introducing bias which will introduce problems in interpreting the

results, the following items should be considered. Both cohort and case-control study methods can be of use.

Cases:
1. an unambiguous case definition;
2. a case-detection method not related to recent immunization;
3. event diagnosis verified by physician blinded to vaccine status.

Well (control) subjects:
1. selection from the same group from which ill children arise, including age-group, living conditions, etc.
2. collection of information in the same way as in cases.

Immunization history:
1. verified from written records, if possible; not obtained only from the parents.

5.3 Aids to evaluation

Suggested steps in the evaluation of reported AEFI's include review of the report, investigation, diagnostic categorization, and classification of probable cause. The classification of probable cause of reported serious adverse events, such as death, requires information collected in the investigations which is as complete as possible. A full clinical description of the timing of onset of each symptom noted, the length of each, results of any health visit assessments and laboratory tests will be needed. In order to allow classifications to be made, the following are some points of evidence that can be used to suggest a probable specific cause, or unknown:

programmatic errors
1. admission of error
2. vial contamination substantiated by laboratory evidence
3. previous problems in administration
4. observed problems in technique
5. reported problems in technique from witnesses
6. laboratory evidence in child
7. vial substitution substantiated by missing vials, witnesses, etc.
8. compatible clinical syndromes (e.g., muscle relaxant)
9. size and/or focality of cluster

inherent risks
1. compatible clinical syndrome
2. other causes ruled out

coincidental
1. not clinically compatible with initial diagnosis
2. event not supported in research literature
3. autopsy or laboratory evidence of other cause

unknown
1. unable to obtain sufficient evidence
2. conflicting evidence

6. AREAS REQUIRING FURTHER DEVELOPMENT

6.1 Field Manual Guidelines

This paper is designed to discuss policy issues and to focus attention on the urgency for initiating and strengthening monitoring systems for AEFI's. A practical guide is required to

deal more specifically with issues related to implementation and follow-up action. A field guide is particularly indicated for and should be designed to help immunization programme managers at state, district and primary health center levels in making decisions regarding field investigations, specific interventions and follow-up measures. The speed with which investigations are conducted and the completeness of the investigations is important. Broad guidelines must be available with the immunization programme managers, before an AEFI has resulted, so that investigations and required medical interventions are applied early.

Some suggestions on the topics to be included in the field guide are made in the following paragraphs. It is recommended that the WHO prepare such a field guide for use or adaptation to suit country needs.

Besides guidelines for investigation and report writing, the field guide should include standard case definitions, differential diagnoses, expected line of treatment and other follow-up measures, laboratories to which samples can be sent and handling of samples, and the channels for reporting AEFI.

The data collected during AEFI investigations can serve many important functions, including better understanding of possible weaknesses in programme implementation, suggesting aspects that require strengthening in training programmes and highlighting areas that might cause public concern and should be addressed in communication strategies. The field guide should provide direction for utilization of the information for improving and sustaining immunization services.

6.2 Training Materials

Several EPI training materials such as modules for mid-level managers, manuals for the peripheral health workers and the Immunization Policy document are available. Such materials contain information of expected mild reactions following immunization and advice on indications and contraindications to immunization. With the declining trend of vaccine preventable diseases and their complications and improved surveillance of AEFI's, the training materials may need to be revised to include some of the severe but rare adverse events.

All moderate and severe AEFI's, such as deaths and illnesses requiring hospitalization, need to be acted upon with urgency and sensitivity. Follow-up action on such reports may be included in the training material for the district immunization programme managers. In areas with high immunization coverage levels and reduced risk of vaccine preventable diseases the concern of the public about severe AEFI's has increased. Therefore, training material must include appropriate public communication strategies.

6.3 Guidelines for Assignment of Probable Cause of an Adverse Event Following Immunization

In general, the classification of an event as probably vaccine-induced versus coincidental will be based on less than fully complete information. Nonetheless, many areas may currently be

performing or will be considering event classification. Guidelines to assist in this analysis must be developed.

A possibility for this classification is to model them on a method recently attempted in the United States, or a simplification of this method. The process consisted of

1. listing the possible diagnoses or aetiologies for the event in a given child;
2. estimating the ratio of probabilities of vaccine causation versus the most likely other cause based on the medical literature, such as in Appendix A; and
3. adjusting the relative probability based on individual characteristics of that reported event.

The method allows for individual analysis of the known facts in making decisions. The approach used is complex, however, and further development may lead to a more practical approach.

6.4 **Research Guidelines**

6.4.1 Etiological Assessment and Risk Factor Analysis

Consensus is desirable as to goals of research in AEFI's needed for public health decisions and in illness definitions. Representatives of several countries in the European Region have recently proposed several common goals related to vaccine-preventable diseases in Europe. Included in their proposals were prospective case-control and other studies of etiological assessment in central nervous system syndromes. WHO can assist in providing a forum for communication of similar research efforts in Europe, North America and other areas, and in derivation of guidelines for studies that will be of use in many areas.

6.4.2 Guidelines for Adverse Event Evaluation of New Vaccines

6.4.2.1 Prelicensure

Clinical field trials of vaccine efficacy generally are designed to examine clinical efficacy while detecting major problems in vaccine safety. These are not generally designed for evaluation of vaccine safety specifically, other than common events. Guidelines are necessary to assist in interpretation of data from clinical studies. These studies should be conducted in collaboration with strong epidemiological input.

Because vaccines are generally applied to more individuals than are drugs, and are commonly administered only healthy individuals, special attention to vaccine safety prior to licensure is critical. However, any powerful study of vaccine safety regarding uncommon events would require tens to hundreds of thousands of participants. Therefore, it is suggested that WHO seek comments on some general guidelines in the assessment of vaccine safety in prelicensure clinical trials. Included in these might be minimal estimates of background frequencies of illnesses of concern, the relative risk or risk attributable to vaccine that is to be detected and the degree of certainty or power that is recommended.

6.4.2.2 Postmarketing

Standardization of AEFI monitoring must be coordinated, particularly among industrialized countries. WHO can assist in coordinating this process.

7. RECOMMENDATIONS

1. All EPI programmes should monitor for selected adverse events following immunization. In most areas, the priority will be to examine events for programmatic errors that can be prevented such as DPT abscesses and reported deaths, due to unknown causes, temporally associated with immunization. In selected areas, more effort can be put into examining less common, purported inherent risks of vaccine.

2. International standardization of definitions of adverse events following immunization is a goal that would benefit field surveillance programmes and research in vaccine safety. WHO should assist this process by convening consensus groups with specific concern for both needs.

3. Field guides should be developed by WHO providing guidance for monitoring and investigation activities recommending similar means of defining and classifying illnesses and follow-up action to be taken.

4. Training materials should be revised to include the basics of conducting, monitoring, and reacting to reports of adverse events following immunization.

5. An eventual goal for all programmes should include routine compilation of information related to adverse events following immunization in the country.

6. With development of this monitoring process in each country programme, WHO should work towards collecting and disseminating programme experiences. WHO should assist in disseminating data currently available from countries already monitoring adverse events following immunization.

7. Guidelines should be derived for studying the etiology of adverse events following immunization and in evaluation of vaccine safety when studying new vaccines.

8. Position papers on quantifying risks and benefits of vaccination should be developed and disseminated by WHO. These should include risk assessment for the common serious adverse events thought to be vaccine-associated.

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Appendix A

ESTIMATED RATES OF ADVERSE EVENTS FOLLOWING IMMUNIZATION

Vaccine	AEFI	Disease (Cases)	Complication Rate/100,000 Vaccine (Immunization)
DPT	Permanent brain damage	600 - 2000	0.2 - 0.6
	Death	100 - 4000	0.2
	Encephalopathy/encephalitis (including seizures, focal neurological signs, coma, Reyes syndrome)		
	Convulsions	600 - 8000	0.3 - 90
	Shock	-	0.5 - 30
Measles	Encephalitis/encephalopathy	50 - 400	0.1
	Subacute sclerosing panencephalitis	0.5 - 2.0	0.05 - 0.1
	Pneumonia	3800 - 7300	-
	Convulsions	500 - 1000	0.02 - 190
	Death	10 - 10000	0.02 - 0.3
BCG	Disseminated BCG infection	-	<0.1
	Osteitis/osteomyelitis	-	<0.1 - 30
	Suppurative adenitis (children under 2 years)	-	100 - 4300

(Source: Galazka AM et al, Bull WHO, 62: 357-366 (1984))

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APPENDIX B

DRAFT PROTOCOL FOR CLUSTER SURVEY FOR BCG LYMPHADENITIS

1. The purpose of the survey is to test in a group or 'lot' of births in a specified area whether the frequency of BCG-associated regional lymphadenitis exceeds 2% of immunized infants.

2. The statistical method used is the Lot Quality Assurance. Random sample of infants is chosen by the standard EPI method of 30-cluster sampling. The clusters are health centres, hospitals and other facilities providing BCG immunization. The expected minimum population size of the area under study is 500,000. The clusters are identified in the same manner as for the vaccination coverage surveys by preparing the cumulative list of number of infants immunized with BCG by each reporting center in the specified period. The cumulative number is divided by 30 to obtain the sampling interval. The first cluster is identified by a random number, the second cluster by adding the sampling interval to the random number and subsequent clusters by adding the sampling interval to the number of the previous cluster.

   Alternatively, if a vaccination coverage survey has been recently conducted in the area, the nearest health center to the cluster village may be selected.

3. Within a given three month period, a day is randomly selected by using a bank note. Full particulars of 14 infants sequentially immunized with BCG from that day, are maintained to enable check-up on return visits for DPT immunization or active follow-up if the child does not return. The children are examined during visits for DPT immunization (if BCG vaccine is administered in the neonatal period) or at nine months during measles immunization for BCG immunization of infants. If the child does not return, a home-visit is mandatory.

   Alternatively, a random day is selected during the period four to six months before the study date. Fourteen infants immunized in sequential order on that day (or following days) are actively followed up after three months to check for lymphadenitis.

4. The mother or other family member is questioned about the occurrence of an enlarged or tender mass or lump under the child's arm on the side of BCG vaccination, and about a draining sinus at that site. The child is examined for a tender mass, lymph nodes at least 2cm in diameter, a fluctuant mass, an enlarged node fixed to the skin, or a draining sinus in the axilla on the side of BCG vaccination. The BCG immunization site is examined for an abscess or tender mass, or a scar over 2cm in diameter suggesting a prior abscess.

5. The sample size of the survey is 400 infants. The cluster forms are compiled at a central office. The observations of first 13 infants in each cluster plus 10 more randomly selected to make 400, are reviewed. A case occurring in the last 20, after 400 infants have been reviewed, should not be counted.

6. If there are three or fewer cases, the true rate of BCG associated lymphadenitis is less than 2% immunized within 96% confidence limits. If cases of local BCG abscesses have also been checked for, and there are three or fewer, the rate of abscess is less than 2%.

(Summarized from the document "Protocol for testing incidence of BCG-associated lymphadenitis" by Gibson JJ et al.)

APPENDIX C

Proposed Adverse Events Following Immunization
For Which Uniform Case Definitions Are Needed

1. **Specific Local Reactions**

   1.1 Bacterial site abscess
   1.2 Sterile site abscess
   1.3 Moderate local reaction
   1.4 Severe local reaction
   1.5 Massive local reaction
   1.6 Local ulcer

2. **Relatively Specific Syndromes**

   2.1 Anaphylaxis
   2.2 Hypotensive-hyporesponsive episodes
   2.3 BCG lymphadenitis
   2.4 Suppurative BCG lymphadenitis
   2.5 Vaccine-associated paralytic poliomyelitis

3. **Non-specific Systemic Events**

   3.1 Encephalopathy
   3.2 Encephalitis
   3.3 Motor seizure
      3.3.1 Simple febrile seizure
      3.3.2 Complex seizure with fever
      3.3.3 Seizure without fever
      3.3.4 Focal seizure
   3.4 Infantile spasms

APPENDIX D

INVESTIGATION OF SEVERE ADVERSE EVENTS FOLLOWING IMMUNIZATION, INDIA

1. The basic principles of field investigations of infectious diseases should be adopted for the investigation of severe AEFI, especially if there is a clustering of cases. Preliminary diagnoses from first reports must be confirmed by a physician. All other children immunized during the particular session must be clinically examined. It is important that non-immunized children of the same age group in the locality are also investigated and examined to exclude temporal relationship.

2. Particularly if the type of AEFI is unexpected and not easily explainable, all signs and symptoms and timing of these must be carefully recorded for review by other experts.

3. Since the primary purpose of investigations is either to exclude programmatic errors or to determine the underlying cause if the reaction was due to a programmatic error, operational aspects of the programme must be carefully reviewed and noted in the written report. Points that need to be specifically examined are procedures followed for collection, storage and issue of vaccines (stock registers and vaccine utilization rates should be checked); methods adopted for the sterilization of syringes and needles, including the total quantities of syringes and needles used during the particular session (it should also be confirmed from the community that a separate sterile syringe and needle for each injection was used); frequency of routine monitoring of services by the supervisor and whether similar reactions had been noted in the past but not reported.

4. Vaccine samples should be sent to the National Control Laboratory. The samples should be sent by courier under proper cold chain conditions. The forwarding letter should explain the circumstances under which the samples were sent. The used vial with the remaining vaccine as well as unused vials of the same batch from the same storage point should be sent.

5. A detailed write-up is necessary as the reports are likely to be reviewed by the state technical committee and perhaps an independent referral group. Uniformity in the format of the reports facilitates review. The report should start with general information regarding the place where the event occurred. The name of the state, district and PHC/ward should be stated. The following points should be covered in the report:

a. General information and details of investigation:

- when the first symptoms were observed, what they were and who reported the event;
- who conducted the investigations and how long after the first symptoms were these started;
- how were the investigations conducted (was active search included, were relevant records checked and whether parents of the child(ren) and other representatives of the community contacted?)
- number of children immunized and the type of reactions observed. The line lists and summary tables should be attached;
- if any unimmunized children in the area had similar symptoms.

b. Clinical aspects for each affected child:

- site of injection of each vaccine and time given;
- detailed clinical picture;
- history of previous doses;
- treatment given;
- outcome of illness
- diagnosis by treating physician and any relevant observation.

c. Operational aspects:

- batch (lot) number(s) of involved vaccine(s)
- how are immunization sessions generally provided in the area. Procedure followed on the day of the event (whether the session was on the scheduled day)
- when and from where the vaccines were received. How were the vaccines stored and transported. Batch numbers of the vaccines.
- how many syringes and needles were available and procedures followed for the sterilization of equipment;
- who administered the vaccines and the training they had received;
- have similar reactions been observed in the past and were not reported.

d. Laboratory investigations:

- name of the laboratory to which samples were sent for testing. Batch numbers of the vials sent. (The test reports are not expected to be available at the time of writing the report).
- any other samples sent for testing; name of the laboratory;

e. Autopsy:

- if a post-mortem was conducted relevant findings may be included.

f. Follow-up:

- state briefly follow-up measures taken

g. Suggestions and recommendations:

- what was the likely cause of the adverse event;

(Date) (Name & Designation)

Note:

1. Each state should have a standing committee of an epidemiologist, a pediatrician and a microbiologist on call to ensure prompt investigations of severe adverse events, especially if a death has been reported. In the event of a death this committee should visit the site and conduct independent investigations within 48 hours. The report of the committee may be looked into by an independent referral group, if necessary.

2. The Director of Health Services should issue a note giving the salient points which should be available to the press for publication. This popular version of the incident should be issued within 72 hours of the incident.

3. Copies of the investigation report (and comments of the referral group) should be forwarded to the Ministry of Health & Family Welfare, New Delhi.